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THE ADVANTAGE OF SERUM THERAPY AS SHOWN BY A COMPARISON OF VARIOUS METHODS OF TREATMENT OF ANTHRAX.

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Various methods of local therapy of anthrax have been in use for many years past, and are still widely employed either alone or in conjunction with other measures. If one has the time to consult the literature dealing with the subject, whether it be in periodicals or in text-books, it is at once evident what wide differences of opinion exist as to the most effective method of treatment. This is unfortunate and is liable to lead one to the conclusion that most all the usual methods give about the same results and it is not therefore a vital matter which one is employed in the individual case. This view-

point must be changed, as there is now accessible certain indisputable facts which prove it to be incorrect. Almost all the measures of local therapy in common use possess too many disadvantages to be considered locally effective, and they are uniformally without claim to a specific effect once an anthrax septicemia has originated. Some of them have even the danger of increasing the possibility of this latter grave complication (septicemia) supervening.

An ideal method of therapy for anthrax is one which fulfils best the following points: (1) It should be appliable to the various forms and locations of the disease; (2) should have the lowest mortality rate; (3) should be as specific as possible; (4) possess no danger of generalizing the local infection; (5) offer the least amount of scarring and deformity; (6) cause a minimum of pain; (7) entail the shortest absence from employment.

To draw any conclusion as to the method which best fulfils these points, the various measures of therapy in use must be first reviewed and their advantages and disadvantages considered.

Thermocautery is one of the oldest methods of treatment known (Schwartz[1]), and despite its many objectionable features it is still widely employed in many parts of the world. It is an extremely painful procedure, and when the lesion is extensive, especially when on the face or neck, it leads to hideous deformity, and prolonged convalescence if the patient recovers. It destroys rather indiscriminately both dead and living tissue, and unless applied thoroughly, which is surely an heroic measure in voluminous anthrax, it may seal off from free drainage tissue which is still infective.

Moreover, the barrier zone to the infection which nature has established may be in part or entirely broken down and generalization may thus originate. The treatment is not in the least specific, and when an anthrax septicemia exists is of no avail. For all these reasons it should be entirely omitted from the therapy of the disease.

Chemical caustics have been widely used in anthrax. Many writers advocate them as the only method of treatment, but in the majority of instances they are advocated as secondary measures. Among the caustics recommended are chloride of lime, nitric acid, zinc chloride, carbolic acid, bichloride of mercury and caustic potash. Graef[2] has reported a mortality of 5 per cent in 38 cases, and Scharnowski,[3] Bidder,[4] Arnozan Laude and Maranger[5] report successful results. The latter three authors, however, have abandoned the procedure owing to the vivid pain which ensues. That the method is uncertain the experience of Morosof[6] shows, for he has been unsuccessful in 2 cases, although in 1 he gave twenty-eight injections of 3 per cent carbolic acid and in the other seventy-six injections of 4 per cent carbolic acid in the depth of the pustule. Amory and Rappaport[7] report 3 recoveries by combined excision and cautery, but in 1 instance it required twenty days for the bacilli to disappear on culture from the lesion, and in another the patient

recovered only after three months. Whitla[8] mentions 2 per cent iodine for local injection and Chauffaud and Boidin[9] report the use of subcutaneous injections of 1 per cent carbolic acid and a solution of Gram's iodine. They admit that the latter solution is horribly painful and both are equally inefficacious.

Chemical cauterization has many of the same contra-indications mentioned under thermocautery. The possibility of poisonous effects or nephritis originating is an additional danger. Superficially applied these caustics are only palliative, and to be in the least effective the application must be thorough, and with many it should be repeated. Their lack of specificity is evidenced also by the diversity of the chemical solutions recommended.

Surgical intervention in the therapy of anthrax comprises two forms—incision and excision.

Incision has fallen in much disrepute as a mode of treatment, especially in Italy and France. Yet it is still often used, both here and abroad, particularly in instances in which the physician fails to recognize the disease and believes he is treating an ordinary carbuncle. The danger of the method was long ago recognized by the French physicians. Guerin,[10] Faucon,[11] Richard,[12] Chambert[13] and more recently Despres[14] warn of the danger of an erysipeloid or purulent inflammation of the wound setting in following operation. It is characteristic that patients treated by incision commonly develop the more severe types of the disease, and not infrequently die. Verneuil[15] gives interesting statistics on this point: "Among 6 patients so treated all died."

Incision has no place in the therapy of anthrax. It is not only contra-indicated but is actually dangerous. The operation breaks down the barrier zone to the infection and opens wide the blood and lymphatic channels of absorption, at the same time failing to remove the infected focus. As a result, increase in the extent of the local involvement and grave possibility of a generalized infection supervening are to be expected. It is also to be remembered that Marchoux[16] showed experimentally in animals that anthrax bacilli multiply rapidly in blood-clots, as they are not then so susceptible to leukocytic activity. Instead of assisting in the cure the operation further endangers the patient's life.

Excision at the present time is the most commonly used method in the therapy of the disease. It is, however, so frequently combined with thermo or chemical cautery or with serum that it is difficult to tell to which the results obtained are mostly attributable. Courtellement and Weill-Halle,[17] Dudley,[18] Ellitrop[19] and Raymond[20] are among the advocates of the method. Dudley combines the treatment with cauterization and serum, as used at Guy's Hospital, London, while Ellitrop administers anthrax vaccine. Some surgeons, among them Paget and Gosselin[21] and Despres,[22] believe that one should never resort to excision no matter what the location of the

lesion. Picaud[23] and Pratorius,[24] the latter on the basis of his extensive experience with anthrax, advise against excision. Müller[25] and Hiss and Zinsser[26] have found it impossible to prevent the spread of the disease in guinea-pigs by immediate excision of the site of inoculation. Scholl[27] recently compared the results obtained by the surgical and non-surgical treatment in 51 cases: 4 (44 per cent) of 9 cases treated surgically died while only 3 (7 per cent) of 42 cases treated non-surgically succumbed. One patient only recovered after amputation at the shoulder-joint. In conclusion, he states "that in several of the surgical cases a rapid increase in edema, a steady decline in the patient's general condition and death several hours later definitely pointed to the operation as a causative factor."

Excision despite its advantages over incision and thermo or chemical cautery has certain outstanding limitations and disadvantages. Thus in anthrax of the face it will always be objectionable from the esthetic viewpoint. Likewise when the neck is involved, if the disease is at all extensive, excision leaves often an extensive surface devoid of skin, with resulting scar-tissue formation and contracture, and, if skin-grafting is not performed, convalescence is much prolonged. The pain of the operation and possible hemorrhage must also be considered. Probably the most frequent source of danger is the difficulty of accurately defining the area to be excised, especially when the edema and induration are marked, as microscopic sections have at times shown bacilli far beyond the exact limits of the pustule in the edematous zone. To excise less than the entire area involved is to subject the patient to the pain and discomfort of the operation without a compensatory result in the way of a certain cure. On the contrary, as Nature's barrier zone is broken down and the blood and lymphatic channels are opened, the danger, local and general, of disseminating the infection is much increased. Since anthrax in man is primarily a local disease and usually remains thus—any treatment which may tend in the slightest way to generalize the infection is scarcely to be looked on as proper therapy. Once a septicemia exists the treatment is only palliative. Then, again, bacilli may persist in the wound for almost three weeks after operation (Rappaport and Amory's case), and in the presence of blood-clots rapid multiplication may occur. For all these reasons the writer believes excision should likewise be omitted from the routine therapy of the disease.

Various other methods have been advised locally in anthrax, many of which are only palliative measures, and some of which are claimed to be somewhat specific. Among the former may be mentioned wet dressings of various antiseptics, as advocated by Verneuil[29] and pulverization with bichloride, as advised by Savini,[30] All these measures evidently exert their action too superficially to be of any direct curative value and are at best only secondary measures. They may provoke inflammation, as Ricaud and

Launoy[28] have pointed out. The value of the subcutaneous injection of oxygen locally into and around the pustule, as recommended by Thiriar[31] and Theiry,[32] has not been established; moreover, anthrax bacilli grow well in atmospheric oxygen. Ramstedt[33] in 7 cases and Müller[34] in 13 have employed symptomatic treatment and rest with complete success. Such measures, while useful adjuncts to a more specific method, cannot be relied on alone, and it represents an attitude of therapeutic nihilism to allow a disease to take its own course if a remedy of proved value is at hand. The use of steam as advocated by Gucciardello[35] is too severe a measure for routine employment and its specific nature is not proved.

In the second group may be mentioned powdered ipecac, arsphenamine, extract of Bacillus pyocyaneus and normal beef serum.

Muskett[36] reports the successful treatment of 50 cases with ipecac paste locally. Both he and Washbourne[37] have experimentally found ipecac to destroy readily anthrax bacilli. This treatment, while not to be relied on alone, owing to what impresses one as a too superficial action, is a useful supplementary measure to a more specific mode of therapy.

Fortineau[38] uses extract of Bacillus pyocyaneus on the basis of antagonism existing between that bacillus and anthrax. He reports 32 cases, with 1 death. Further reports are necessary to establish the value of this local method. It has not been proved to be effective in anthrax septicemia, and the question of its value in the more virulent types of the local disease is still to be settled. It is not usually accessible for use, which is another disadvantage.

Arsphenamine has experimentally been proved of value by Shuster and Laubenheimer,[39] Laubenheimer[40] and Becker.[41] Each reports a recovery in septicemic cases with the drug. The results are encouraging but the treatment is in its experimental stage.

Normal beef serum has been advocated by Kraus, Penna and Cuenca.[42] They report a total of 415 cases with 4.3 per cent deaths. In the last 180 cases treated there were 11.6 per cent deaths, or 3.4 per cent, omitting intestinal cases. Lignieres[43] denies the value of beef serum in anthrax and reports experiments to prove his contentions. Kolmer[44] has also recently shown that while beef serum contains some antibactericidal properties it is without demonstrable protective and curative value in experimental infections in mice and rabbits.

Hutyra[45] has proved that immune anthrax horse serum gives higher protection in test animals than normal serum. In a recent article[46] in current literature the value of beef serum is again repudiated. Therefore Kraus's contention must still be accepted with reserve until such a time as normal beef serum has been shown to be experimentally and practically as effective as anthrax serum. In the absence of immune serum, normal serum may be tried until the former is obtained.

Anti-anthrax Serum. The credit for the original production of this serum is due to Marchoux, of France, and Sclavo, of Italy, both investigators publishing their work in 1895. Marchoux succeeded in immunizing sheep to anthrax by use of attenuated cultures, according to the method devised by Pasteur, Chamberland and Roux, and then by hyperimmunization with virulent cultures, in increasing doses at intervals of a week, obtained a serum possessed of both prophylactic and therapeutic properties.

Marchoux[46] showed that an immune sheep serum of (1–200 titer) was curative for rabbits in doses of 7 c.c. when it was inoculated at the same time or seven hours after the subcutaneous inoculation of $\frac{1}{2}$ c.c. of virulent anthrax culture. It was likewise effective in preserving life in 10 c.c. doses when it was injected twenty-four hours after the virus.

Sclavo,[47] working along somewhat similar lines to Marchoux, using, however, larger animals, at first goats and later asses, succeeded in producing a potent serum for use in human cases of the disease. As recently prepared, 10 c.c. of the serum thus obtained protects a rabbit from 0.5 c.c. of fresh virulent broth culture. Sclavo immunizes his animals over a long period of time, often as long as two years. Sobenheim[48] has modified the original methods of immunization further by employing simultaneous inoculations of anti-anthrax serum and culture, the latter being at first attenuated and later highly virulent, and given in increasing amounts until the animals (sheep) could withstand enormous doses. The serum was injected on one side of the animal's body and the virus on the opposite side. The serum obtained thus had the usual prophylactic properties for experimental animals (rabbits) in 10 c.c. doses, and also protected non-immune sheep (2 out of 5 animals) inoculated with a virulent anthrax culture in doses of 40 c.c. given from ten minutes to six hours after the cultures. Sobenheim used his method of immunization with complete success in a herd of 2700 cattle without any deaths or ill-effects attributable to the inoculations and with the complete disappearance of any further cases of anthrax among them.

Sclavo serum has been used extensively in Italy and South America both prophylactically and therapeutically in cattle and also in the treatment of the disease in man. It has, however, been very little employed in this country, and it is only in the last few years that the serum treatment of anthrax has come at all into use in the United States. The more frequent employment of immune serum in human cases of the disease is in no little part due to the fact that for the last few years the Bureau of Animal Industry in Washington has been preparing and has been distributing on request a very potent anthrax serum.

The credit for the perfection of this very potent serum is due to Dr. A. Eichhorn,[49] formerly chief of the bureau, and his collaborators.

In an attempt to find a more satisfactory method of immunization than those now in use they resorted to combined immunization with potent anthrax serum and carefully standardized spore vaccine, and found this method to possess marked advantages over the older Pasteur method. (The Pasteur method possessed certain hazards either in that the vaccine was too weak to protect or too virulent to be safely used[50]). During the progress of the work repeated occasions arose to treat a considerable number of afflicted animals with the serum thus produced, and remarkable recoveries were obtained in a very high percentage of the cases, including some of the more severe types. Comparative tests were made of this serum and several of the European makes and the American product was revealed to be twice as potent. The serum has been shown to have great therapeutic value in malignant pustule in man. Later by an improved technic, modelled along that which Banzoff used for diphtheria antitoxin, success was attained in fractioning and separating off the globulin content which contains the concentrated antibodies. This globulin serum has also proved its potency both in numerous tests on laboratory animals and practically in larger animals—cattle and horses.

The Bureau of Animal Industry has been furnishing state and city hospitals with the serum upon request for several years past, but in a recent communication from the bureau the writer learns that it is not their intention to continue this practice, inasmuch as several of the biological firms are now prepared to furnish such a product.[50]

Statistical Study of Anti-anthrax Serum. Picaud[23] believes that anti-anthrax serum has an incontestable efficacy, and to prove this refers to statistics of Pagliani.[51] In Italy from 1890 to 1900 there were recorded 24,052 cases of anthrax with 5812 deaths, or 24.16 per cent. On the contrary, statistics of these late years during which serum was used show 160 cases with 10 deaths, or 6.25 per cent, and in these 10 cases Pagliani states that the serum was employed too late to expect anything of the treatment. In 130 cases observed in Argentine Republic and treated by Sclavo[23] serum the mortality is considered by the writers as reduced to zero, the few cases that happened to die being attributable to secondary infection. In 1903 Sclavo[52] reported 164 cases treated by serum with only 6.09 per cent of fatalities. Legge[53] collected 12 cases of anthrax treated by serum in England between 1904–1905. Of these, 4 were treated by serum alone, 3 recovered and 1 died; while of 8 treated by serum plus excision, 6 recovered and 2 died. Of the fatal cases the serum was not administered until the day of death in one case and in the other case not until twenty-four hours before death, the dose being only 20 c.c. in the latter.

Herley[54] has reported 8 cases of anthrax treated by Sclavo serum with 1 death, excision being performed also in all but 1 instance.

Royer and Holmes[55] have reported 15 cases of anthrax, 4 of which were treated without serum with 1 death, and 7 by Sclavo serum plus surgical intervention with 1 death. These 11 cases comprised the more serious in which the lesion was located on the face or neck, while in the remaining the extremities were involved 3 out of 4 times. Schwartz[1] has collected a series of 68 cases occurring in New York state. His statistics show 17 cases treated by serum and rest with 5 deaths and 12 recoveries, and 28 cases treated by serum and excision, in one of which excision was close, with 26 recoveries and 2 deaths. Page's[56] statistics from English cases of anthrax threated with serum show an apparently higher mortality than in untreated cases. In the earlier group of cases the apparently high mortality was due to use of too small doses (10 to 20 or 30 c.c.), and in the later group the serum was often administered *in extremis*.

Pied,[57] in 1913, states that up to that date he found reports of 7 cases of anthrax with generalized blood infection which had recovered following scrotherapy and 2 in which serum was used without success. Bandi,[58] in 1904, reported 2 remarkable cases of recovery in patients with an anthrax septicemia following energetic serum therapy. The first patient had been ill four days with a lesion on the forearm treated by thermocautery, and although the latter was thoroughly applied the process rapidly advanced, and when Bandi was called the man was comatous, with a temperature of 104° and a cloud of albumin and casts in the urine; 150 c.c. of serum was given immediately intravenously and 50 c.c. more the same evening. One and a half days later the temperature was normal, the patient conscious, the blood culture negative, the urine cleared up and the edema confined to the pustular zone. The second case was very similar and equally remarkable. Becker,[59] Bissell[60] and Graham and Detweiler[61] have each reported a case of malignant pustule with septicemia which recovered following the use of anti-anthrax serum. In the case of Graham and Detweiler excision was performed on the fourth day of the disease but failed to control the malady. In fact, within twenty-four hours afterward the blood culture became positive. On the sixth day 80 c.c. of anthrax serum and 100 c.c. of chloramin-T (Dakin) were given intravenously and complete recovery ensued.

Selavo, Buron and Jager and Becker[62] have also demonstrated that anthrax serum is an efficient means of cure of even an anthrax septicemia in which the mortality by any other method is 100 per cent. All agree that under the influence of serum intravenously the bacteria rapidly vanish from the blood stream.

Rappaport and Amory[7] have reported a severe facial case with marked edema recovering rapidly after 80 c.c. of serum intravenously. Armour[63] cites an interesting case in which serum was not used until the seventh day of the disease, when the patient was in danger of suffocation. Within four days the patient was convalescent. A total of 60 c.c. of serum was given.

Mendez[64] has reported 1073 cases of anthrax with a death rate of 4.19 per cent treated by means of a serum he prepared himself by a method similar to that of Sclavo, the fatalities being due in the few fatal cases to the use of serum in moribund patients, to edema of the glottis, to myocarditis, to atheromata or to alcoholism.

Legge[53] in his very thorough article has examined the details of all published cases he could find up to January, 1905, treated by serum, namely, 67 in number. Of these, 56 were treated by serum alone and 11 by serum and some other treatment with a total death rate of 9 cases. In 44 of the 56 cases in which details would allow conclusions, marked improvement had taken place not only in the general symptoms but in the arrest in the further development of the pustule and in diminution of the edema by the third day. The average duration of treatment in these 44 cases was eight days. In none was it more than fourteen days. No visible scar or only a slight scar was present in all cases except 2, in which there was some loss of tissue, despite the fact that the face and the neck were involved in 35 of the 44. In 7 of the 9 fatal cases the patients were in a serious condition with widespread edema when the serum was administered and in all death occurred within thirty hours, usually in twelve, after the serum was given. Moreover, the doses of serum used in fatal cases were small, usually 20 to 30 c.c., and only one dose was given, and that apparently subcutaneously. In only 2 cases was the dose repeated a second time.

Cicognani[65] reports some remarkable facts in connection with the serum treatment. In Santa Croce, in Italy, a town of 5000 inhabitants with 36 tanneries, where Cicognani has adopted the serum treatment exclusively, the workers now insist on having this treatment to the exclusion of every other, and since operative interference is unnecessary, present themselves when there appears the smallest pimple suggestive of anthrax. Cigognani remarks on the rapidity with which improvement in the general condition occurs, often within a few hours, and the pustules dry up within a few days, while convalescence is much shortened. Lockwood and Andrews[66] and Stretton[67] have each reported a successful case treated by serum. In each instance the lesion was on the face and excision was contraindicated from an esthetic standpoint. The writer[68] has previously reported 2 cases and has since treated 5 more successfully by Eichhorn serum. The recovery in all instances was extremely rapid; convalescence was established within a few days after serum treatment was begun. The pustule in all instances rapidly dried up in a minute and a almost invisible scar was the only remains of the disease. The specific influence of the serum was so marked as to leave no question in the minds of the observers of the value of the treatment. The lesion was not excised in any of the 6 cases. Ascoli,[69] of Milan, uses serum often as the only treatment in doses of 5 to

15 c.c., sometimes repeating the injections five or six times in the same day. Sclavo[70] has lately stated that doses of 10 to 50 c.c. of serum are too small and that 60 to 80 c.c. is a minimum. Many authorities advise 40 c.c. Pagliani[51] has drawn certain conclusions in regard to treatment by anthrax serum: (1) The serum even in large doses is absolutely innocuous; (2) it is well supported even if given intravenously; (3) it may save the patient when the prognosis is hopeless; (4) it arrests rapidly the local process and reduces to a minimum the destruction of tissue.

Modat[71] believes in the efficacy of the serum treatment of anthrax and uses doses as high as 60 c.c., repeating the injection in twenty-four hours in doses of 20 to 30 c.c. and continuing this until the disease is controlled. Modat states that veterinarians sometimes use as much as 500 c.c. to 600 c.c. of serum at one dose in anthrax infections in horses. He quotes the work of Cuica in Bucharest, who has prepared an immune serum and relies on it exclusively in therapy. This writer has reported 40 cases, in 6 of which serum was not used, with 100 per cent mortality, the remaining 34 all recovering under serum therapy.

Dr. Douglass Symmers,[83] director of the Laboratories at Bellevue Hospital, reported recently "that within the past few years some 15 cases of anthrax have been treated in that hospital with specific serum and the results have been very gratifying; that while as one readily understands, all of the cases which had become septicemic with anthrax bacilli when first seen died, those which came under the serum treatment early were speedily cured, good results being apparent within forty-eight hours and recovery taking place within a week or ten days." The method of treatment followed has been to give 40 c.c. of Eichborn serum intravenously every four hours, and at same intervals to inject 10 c.c. into the skin surrounding the pustule. Excision which was formerly used as a routine with serum or alone has been abandoned.

The reported cases of anthrax in New York City in the last few years have been as follows:

Year.	Cases.	Deaths.
1915	13	9
1916	4	3
1917	16	9
1918	15	4
1919	14	9
1920	12	1

During the early years of this period, 1915, 1916, 1917, serum was little, if at all, used. During the following years it began to be more employed but was combined usually with other methods of treatment, mostly excision. Finally, during 1920 serum has been fairly uniformly used and excision has been given up by many hospitals.

Hubbard and Jacobson[85] summarize the treatment in the 34 cases that have occurred in New York City during 1919 and 1920. The table is as follows:

	No. cases.	Recoveries.	Deaths.
Anti-anthrax serum only	14	12	2
" " " and incision	5	4	1
" " " and excision	4	3	1
" " " and chemical cautery	2	0	2
Chemical cauterization and incision	2	1	1
Anti-anthrax serum, excision and chemical application	1	1	0
Chemical application	1	1	0
" " yeast	1	1	0
No treatment recorded	4	0	4

Hubbard and Jacobson comment upon therapy thus: "As 14 cases recovered without operation and 9 recovered with operation it would be logical, to judge from the observed cases, that it was best not to operate. Again, out of the 14 that received only anti-anthrax serum 2 died. Out of the 12 that received serum aided by other treatment 4 died. The method which seems most successful is that of administering anti-anthrax serum, 10 c.c. by local infiltration every eight hours and 40 c.c. intravenously every four hours."

Comment on Serum Therapy. From the review of the statistics just quoted I believe certain conclusions may be drawn. From the standpoint of mortality in very large series of cases, anthrax serum has evidently the lowest death-rate of any treatment. Still there are very low mortality rates reported in fairly large but isolated series of cases by other methods, such as those of Kraus and his collaborators with normal beef serum, of Graef with caustic potash, of Muskett with powdered ipecac, and of Fortineau with extract of Bacillus pyocyaneus. Mortality alone however is not the only factor to be considered in selecting the ideal method of therapy for anthrax; other points previously referred to must also be considered.

At first, offering as it did a new method of therapy, anthrax serum was used like diphtheria antitoxin in the more desperate cases, often very late in the course of the disease, and this fact accounts for many of the early non-successes. Relatively few failures have occurred with immune serum which cannot be traced to either of the following facts: (1) To its use too late in the course of the disease within twelve to twenty-four or thirty-six hours of death; (2) to the employment of too small doses (20 to 30 c.c.); (3) failure to repeat the injections frequently, say every six to twelve hours; (4) use in persons with chronic disease, such as alcoholism, syphilis, chronic nephritis, myocarditis, etc.

The number of recoveries in cases that are considered hopeless is a most important comparative test of any measure of therapy. In anthrax septicemia immune serum has given the highest number of successes. In internal anthrax it should always be used, as it is

the only instrument of treatment worthy of the name, and we have yet to see what may be accomplished with a potent serum used properly. It is to be recalled that Mitchell[72] has seen cases presenting all the symptoms of pulmonary anthrax recover under serum therapy.

Immune serum therapy fulfils best the points mentioned as requisite for an ideal method of therapy. It offers the least pain, a minimum of scarring and is appliable to all forms and locations of the disease. It entails a shorter absence from employment than any other method with the exception possibly of excision. The serum is specific and is the only safeguard we have against generalization of the infection.

In this country we are especially fortunate in having accessible for the past few years a serum possessed of strong therapeutic properties as that prepared by the Bureau of Animal Industry. On the basis of the experimentally proved prophylactic value of this anthrax serum, as well as its incontestable efficacy in the treatment of the disease in both man and animals, there is now no longer any excuse for failure to utilize it in the treatment of all forms of anthrax, but especially of malignant pustule, in which the mortality can probably be reduced to a negligible one by early diagnosis and prompt serum therapy.

The specific action of the serum upon the course of the disease will rarely be questioned by those who have had an opportunity to employ a reliably potent preparation. Examples have been cited above which illustrate this, and they might be multiplied if space allowed. The prompt subsidence of constitutional symptoms, sometimes within twenty-four hours, and the rapid improvement in the local lesion, often within a few days, are the rule and not the exception. Statistics adverse to serum therapy are impossible to find if Page's[56] reports be excluded.

An argument that has been advanced against the use of serum is the expense of the treatment. Thus $30 has been quoted as the cost of production of the amount of serum required for the initial dose. Eichhorn[73] states that at present the serum sells at the rate of 5 cents per c.c., so in this case the initial dose should not cost any more than from $5 to $10. At this rate the entire cost of the treatment for an average case would not exceed by much the figure previously given by some writers as cost of the initial dose.

General Administration of Serum. The essential aim in the administration of serum is threefold: (1) To bring about a subsidence of the local lesion; (2) to counteract whatever toxemia may exist; (3) most important of all, to anticipate and prevent the development of an anthrax septicemia, or to try to control the blood infection if it exists when treatment is begun.

An outline of a method of administering anthrax serum, including the dosage and interval between doses in the various types of the

disease, may be of practical use, as the writer has been unable to find any such plan in the literature reviewed. It is perfectly logical that a severe or septicemia case requires larger and more frequent doses than a mild case.

At the beginning of treatment a blood culture should always be taken. The result gives one an index of the severity of the case and of the extent to which serum must be pushed. During the interval elapsing before the result of the blood culture is known, usually twenty-four hours' treatment must be energetically pursued in all cases, even the mild and moderate ones, because occasionally constitutional symptoms may be misleading as to the existence of a septicemia. Whether in all cases in this interval of twenty-four hours it would be best to follow the method of Symmers,[83] to give 40 c.c. every four hours, remains for later studies to show. The writer believes, however, that at present the following may be submitted as a tentative plan:

In Absence of Anthrax Septicemia. 1. In mild cases of the disease with little constitutional disturbance and a small well-circumscribed lesion with little edema the serum need not be given more often than every eight to twelve hours and commonly not more than three or four injections of 50 c.c. each (Eichhorn[74] recommends 50 c.c.) intravenously in the first twenty-four hours are required. The subsequent injections may be given at twelve to twenty-four hours' interval, depending on the progress of the case, commonly not more than six injections being required, the last few intramuscular or subcutaneous. Local serum therapy, as described below, should be used every twelve to twenty-four hours.

2. In the moderate cases, with medium-sized lesion and a moderate degree of edema and induration associated with definite constitutional symptoms, the serum should be administered for the first twenty-four hours by intravenous injections in doses of 50 to 80 c.c. (Eichhorn[74] recommends 50 to 100 c.c.) every eight hours, the subsequent treatments and frequency being in accordance with the progress of the case, commonly not more than six to eight injections being required, the last two or three intramuscular or subcutaneously. Local serum therapy should be employed for the first few days every twelve hours.

3. In severe cases, with large, voluminous lesions and extensive edema with or without marked constitutional disturbance but with negative blood culture, the serum should be administered by an intravenous route, either in small doses frequently repeated, 40 c.c. every four hours, or in larger doses at less frequent intervals, 80 to 100 c.c. (Eichhorn[74] recommends 100 to 200 c.c.) every six to eight hours for three or four more injections until the disease is controlled, when the intramuscular or subcutaneous route may be used in part and the doses reduced to 50 c.c. at intervals of twelve to twenty-four hours. Local serum injections should be given every six to eight hours for the first few days.

In Septicemic Cases. In such instances with a lesion as just described we have to deal with a most fatal disease, and it seems to be the consensus of opinion that the use of serum must be in unusually large doses and frequently given, the treatment being energetically continued until after the blood culture is negative. In such cases the injections would appear to be indicated every three or four hours intravenously in doses of 100 to 150 c.c. (Eichhorn[74] recommends 200 to 300 c.c.), and this treatment is continued until the septicemia is checked or the patient succumbs. Salvarsan may yet prove a useful adjunct in these desperate cases. The injection of serum locally should also be given every four to six hours.

In internal anthrax it would seem that a similar method of therapy to that used in septicemic cases would be in order. Anthrax serum should likewise be used intraspinally in anthrax meningitis.

Local Serum Therapy. It is evident in the review in the first part of this article that while many writers advocate diverse methods of local therapy, *i. e.*, cauterization, incision, excision, injection of chemicals, application of steam vapor, etc., a considerable number have combined these measures with serum therapy, evidently not trausting to them alone to bring about a cure. Since the only danger of the disease, rare cases of suffocation excepted, is the dissemination of the infection into the blood stream, the question of the advisability and necessity of these measures comes up. The prime essential in successful treatment is evidently to guard against blood infection, and this may be accomplished by (1) the general (intravenous and intramuscular) and local administration of immune serum, and (2) by avoiding the use of any local measure of therapy which might tend to generalize the local disease.

The measures of local therapy in common use are so severe and have so many disadvantages, such as pain, scarring, disfigurement and danger of disseminating the infection, to which attention has been called in detail above, under their appropriate headings, that the writer[68] in treating his own cases hesitated to resort to any of them. The only measure recommended which seemed to have no disadvantages and be of some therapeutic value, but probably more palliative than curative, was the application of wet dressings of powdered ipecac. This was therefore tried. In order to obtain an additional and more active and probably effective measure of local therapy it was decided to try the effect of the injection of serum into the lesion itself.[68]

It was considered probable that the introduction of the serum into close contact with the pustule would not only possess great advantages over other local methods previously advised but would actually be an additional precaution against an anthrax septicemia thus originating and might well have a decidedly beneficial influence upon the evolution of the lesion. As previously reported,[68] the method consisted in the injection of 2, 2.5, or even 3 c.c. of serum

at each of three or four points equidistant from one another at the various sides of the pustule. The needle is best inserted into the red indurated border of the pustule just beyond the blanched zone, the serum being directed toward the base of the eschar and injected so as to circumscribe the lesion. The injections are given once, twice or three times in the twenty-four hours, depending on the severity of the case, and not more than 7 to 10 c.c. are injected at one time. Commonly four to six injections suffice. A 5 c.c. glass Leur syringe and a fine-gauge needle are used in giving the treatment. The method has proved practically successful as the most desirable measure of local therapy. The writer has reported 2 cases previously and has subsequently treated 5 cases, all terminating in recovery despite the fact that the pustule was located either on the face or neck in all instances.

Local use of serum theoretically seems logical. The serum is then supplied in a most concentrated form at the site of the infection. The importance of this fact has been previously expounded on by Flexner[75] in relation to various bacterial inflammations situated in locations in which they receive a diluted and modified lymph secretion, as in massive inflammations, abscess formations and infections of serous cavities. While anthrax is not mentioned by Flexner in this excellent treatise[75] on *Local Specific Therapy of Infections*, the similarity to a massive inflammation and abscess formation is obvious. As examples of previous local use of serum in infections certain facts may be cited. Speiss[76] has shown that incisions infected with virulent streptococci have been controlled in the rabbit more surely by the application of the corresponding antiserum locally to the wound than by injecting it intravenously. Romer[77] has shown that pneumococcus keratitis is benefited by the direct instillation of antipneumococcus serum into the eye. Likewise, Netter[78] has recently succeeded in preserving vision by the injection of antimeningitis serum into the vitreous chamber of the eye in a case of epidemic meningitis complicated by suppurative choroiditis, a complication always resulting in loss of vision.

The character of the local inflammation in anthrax is of a peculiar type.[79] The serous discharge from the pustule during the first several days of the disease and often until the end, especially in fatal cases, is characteristically poor in leukocytes. The pathological anatomy of the lesion, as shown by Cornil,[80] Wagner[81] and Straus,[82] shows a very definite tendency for segregation of the anthrax bacilli in the center of the pustule, in which they are intertwined in a compact network practically free of leukocytes, the latter being distributed most densely as diffuse infiltration at the margins of the lesion and in the subjacent cellular tissue. In the more malignant cases and in the early stage of the disease, phagocyte activity is not much in evidence. Since the serum has been shown to have a marked effect in facilitating phagocytosis (Mar-

choux[16]) it is evidently logical to supply it in a concentrated form at the site of the pustule. In this way the normal resistant processes are strengthened, phagocytosis is increased and the inflammation is more quickly terminated.

The writer is glad to say that Symmers,[83] of Bellevue, has recently adopted the local serum therapy of anthrax as described above and reports very satisfactory results. Graham,[84] whose experience with anthrax has been quite extensive, in a recent article also endorses local serum therapy, and comments on the success that has attended its use when combined with the intravenous administration of serum.

Summary. 1. The various measures of therapy in use in treatment of malignant pustule have been reviewed. Statistics have been quoted showing comparatively the mortality with different treatment.

2. The disadvantages of the various measures of local therapy in common use have been discussed and attention has been drawn to the dangers that many of them possess.

3. The history of the development of anti-anthrax serum has been outlined. All the available statistics and facts relative to serum therapy of the disease in the foreign and domestic literature have been quoted so that conclusions might be drawn as to the value of the method. With marked uniformity reports of those who have used immune serum are favorable to the method.

4. The advantages of serum treatment over the other methods have been outlined.

5. A plan of dosage and interval between doses in the various forms of the disease has been tentatively given.

6. Local serum therapy has been described as a method of local treatment to replace the older and more dangerous measures. Its practical application and theoretical basis have been discussed.

Conclusions. 1. The measures of local therapy of anthrax in common use should be abandoned, owing to the disadvantages or even dangers they possess. These disadvantages include scarring and disfigurement, pain, danger of secondary infection being introduced, liability of spreading the disease locally or into the circulation, prolongation of convalescence and, but most important of all; their lack of any specific effect upon the course of the malady and their uselessness when the pustule is voluminous and when a septicemia has originated. The pustule is best left to its own evolution rather than to employ the more radical measures, owing to their tendency to disseminate and generalize the local disease, while the palliative measures exert their effect entirely too superficially for any direct curative value.

2. The value, both prophylactic and curative, of anti-anthrax serum must now be regarded as established by statistics. Its well-nigh specific nature in the therapy of the disease must be recognized

by the profession. The mortality from malignant pustule will be reduced to a minimum by prompt recognition and early serum treatment.

3. No case of anthrax septicemia should be considered beyond hope until intensive serum therapy has failed.

4. The serum prepared by the Bureau of Animal Industry or according to their method has been proved of marked potency, being according to certain reports twice the strength of the European preparations.

5. As originally described by the writer, the local injection of anthrax serum into the pustule is apparently the most effective means of local therapy and should always be used as a supplementary measure to the general administration of serum.

6. Anthrax serum fulfils best the points requisite for an ideal method of treatment of anthrax: (1) It is appliable to all forms and locations of the disease; (2) yields on average the lowest mortality rate; (3) is a specific measure; (4) is a safeguard against generalization of the local disease if used in time; (5) offers the least amount of scarring and deformity; (6) causes a minimum of pain; (7) demands on an average the shortest absence from employment.

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